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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/725,064	12/01/2003	Marshall L. Summar	02-40052-US-P (848966.201	2736

7590 08/11/2005

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EXAMINER	
LEWIS, AMY A	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 08/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/725,064	SUMMAR ET AL.	
	Examiner	Art Unit	
	Amy A. Lewis	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/25/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152),
6) ☐ Other: _____.

DETAILED ACTION

Status of the Case

Priority to Applicantion No. 10/122,445, filed 12 April 2002, is acknowledged. Claims 1-25 are currently pending in this application.

Claim Rejections - 35 USC § 112, 1st paragraph
Scope of enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1) Claims 1-20 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of hepatic encephalopathic episodes, does not reasonably provide enablement for prevention of hepatic encephalopathic episodes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The burden of enabling the prevention of a condition such as hepatic encephalopathic episodes would be much greater than that of enabling the treatment of the condition. In the instant case, the specification does not provide guidance as to how one skilled in the art would accomplish the objective of preventing hepatic encephalopathic episodes or how a patient could be kept from every being susceptible to this condition. Nor is there any guidance provided as to a specific protocol to be utilized in order to show the efficacy of the presently claimed active agents for preventing hepatic encephalopathic episodes.

The term "prevention" is synonymous with the term "curing" and both circumscribe methods of absolute success. Since absolute success is not reasonably possible with most diseases/conditions, especially those having etiologies and pathophysiological manifestations as complex as hepatic encephalopathic episodes, the specification, which lacks an objective showing that hepatic encephalopathic episodes can actually be prevented, is viewed as lacking an adequate written description of the same.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) Nature of the invention.
2) State of the prior art.
3) Level of predictability in the art.
4) Relative skill of those in the art.
5) Amount of direction or guidance provided by the inventor.
6) Presence or absence of working examples.
7) Breadth of the claims.
8) Quantity of experimentation necessary to make or use the invention based on the content of the disclosure.

The instant specification fails to provide guidance that would allow the skilled artisan to practice the instant invention without resorting to undue experimentation, as discussed in the subsections set forth hereinbelow.

1) The nature of the invention.

The claimed invention relates to a method of preventing hepatic encephalopathic episodes.

2) State of the prior art & 3) Level of predictability in the art.

While the state of the art is relatively high with regard to the *treatment* of hepatic encephalopathic episodes, the state of the art with regard to *preventing* hepatic encephalopathic episodes is underdeveloped. Hepatic encephalopathy is associated with hyeprammonemia, which is caused by a variety of pathologies, and results in ammonia neurotoxicity (See Majeed KI, *Hyperammonemia*, eMedicine, Internet Access to the Minds of Medicine, December 18, 2001, printed on 5/21/03 from <<http://www.emedicine.com/NEURO/topic162.htm>>, see p. 2, 5-13; and Harrison's Principles of Internal Medicine 10th Edition, pages 125, 1775, 1781, & 1814-1816). In particular, Harrison's states that "the exact chemical mediators of hepatic enchphalopathy remain unknown" (p. 1775) and no single biochemical or physiological defect has been shown to be the actual cause of hepatic encephalopathy" (p. 1814). Majeed and Harrison's cite several different treatments, including lactulose, neomycin and dietary protein restriction (Harrison's p. 1816) and sodium benzoate or phenylacetate (Majeed p. 15).

In addition, the level of predictability regarding outcome of treatment of hepatic encephalopathy is unpredictable, see Table 1 (p.683) of del Rosario et al. ("Hyperammonemic enchepalopathy after chemotherapy," *J Clin Gastroenterology* (1997) 25(4): 682-684), cited by Applicant on PTO form 1449.

The lack of significant guidance from the present specification or prior art with regard to the actual prevention of hepatic encephalopathic episodes with the claimed active ingredients makes practicing the claimed invention of prevention unpredictable.

4) Relative skill of those in the art.

The relative skill of those in the art is high, generally that of a PHD/MD with several years of practical experience.

5) Amount of direction or guidance provided by the inventor & 6) Presence or absence of working examples.

The specification teaches the specific treatment of hepatic encephalopathy in a group of six patients suffering from moderate to severe hepatic encephalopathy, due to a variety liver diseases, with sodium phenyl butyrate (see specification paragraphs [26-36]). However, it does not teach prevention or the use of any of the other compounds listed in claim 1. It should also me noted that this treatment group is currently "suffering from" hepatice encephalopathic episodes, therefore they have already had an "initial episode" (such as recited in instant claim 1), so the hepatic encephalopathy is past the point of initial prevention.

In addition, the example provided by the instant specification at paragraphs [26-36] is written in a manner that it appears be a prophetic example, as opposed to a working example with clinical data. See MPEP § 608.01(p), part II on Simulated or Predicted Test Results or Prophetic Examples.

7) Breadth of claims.

The claims are very broad and inclusive of prevention of hepatic encephalopathic episodes in general. The breadth of the claims exacerbates the complex nature of the subject matter to which the present claims are directed. The claims are extremely broad due to the various pathologies which can result in the condition.

8) Quantity of experimentation needed to make or use the invention based on the content

of the disclosure.

The specification does not enable any person skilled in the art to which it pertains (i.e. prevention of hepatic encephalopathic episodes) to make or use the invention commensurate in scope with the claims. The lack of adequate guidance from the specification or prior art with regard to the actual prevention of all episodes of hepatic encephalopathy brought on by various pathologies fails to rebut the presumption of unpredictability existent in this art. Applicants fail to provide the guidance and information required to ascertain a treatment which will prevent such episodes without resorting to undue experimentation. Applicant's limited disclosure with respect to sodium phenylbutyrate (see specification at paragraphs [26-33]) is noted but does not demonstrate prevention of hepatic encephalopathy.

Absent a reasonable *a priori* expectation of success for using a specific compound/agent to prevent hepatic encephalopathic episodes, one skilled in the art would have to extensively test many various tumor types of compounds under various conditions and degrees of severity of hepatic encephalopathy. Since each prospective embodiment, and indeed future embodiments as the art progresses, would have to be empirically tested, and those which initially failed tested further, an undue amount of experimentation would be required to practice the invention as its is claimed in its current scope, because the specification provides inadequate guidance to do otherwise.

Claim Rejections - 35 USC § 112, 2nd paragraph
Indefiniteness

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2) Claims 3-10 and 12-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3-5, 12-15 recite the dosing units $g/m^2/day$. It is unclear as to how much is being administered according to this unit of measure. As it reads, it appears to be grams per meter squared of body surface area per day. In the specification at paragraph [33] dosages are measured in mg/kg, then they are measured in g/m^2, without clarification of what this unit means. For the purposes of examination, g/m^2 will be interpreted as g/kg, and $g/m^2/day$ as g/kg/day. Appropriate correction and clarification is suggested.

3) Claims 22 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: criteria for determining whether a hepatic encephalopathic episode has been delayed versus not delayed and a means of measuring the delay of onset of the episode.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4) Claims 1-6, 8-16, and 18-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Majeed KI (*Hyperammonemia*, eMedicine, Internet Access to the Minds of Medicine, December 18, 2001, printed on 5/21/03 from <<http://www.emedicine.com/NEURO/topic162.htm>>, p. 1-22).

Majeed teaches that increased entry of ammonia is a primary cause of neurological disorders associated with hyperammonemia, such as congenital deficiencies of urea cycle enzymes, hepatic encephalopathies, Raye Syndrome, several other metabolic disorders, and some toxic encephalopathies. (See: page 2, paragraph 2). The reference teaches sodium benzoate (of instant claims 8, 10, 18 and 20), sodium phenyl acetate (of instant claims 9, 10, 19, and 20), and sodium phenyl butyrate (of instant claims 6 and 16) as urea cycle disorder treatment agents, thus meeting the limitation of the specific agents. The reference also teaches these agents in amounts ranging from 0.15mg/kg/day to 13 g/kg/day, which overlap those of instant claims 3-5 and 12-15, and administered in intravenous form or with meals in powder or tablet form, thus meeting the limitations of oral and parenteral administration of instant claims 2 and 11 (see: pages 15-18). Regarding the limitation of a method of preventing an initial hepatic encephalopathic episode (of instant claim 1), according to the instant specification (at paragraphs [15-17]) "preventing" can

include preventative measures, which is equivalent to a method of treating. In addition, a method of "lessening the severity of" (of claims 21 and 23) or "delaying" (of instant claims 22 and 24) an encephalopathic episode is also a method of treatment. Absent evidence to the contrary, an equivalent outcome is taught by the prior art.

5) Claims 1, 2, 3, 7, 11, 12, 13, 17, 21, and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Brusilow (US Pat. 5,968,979).

Burusilow teaches phenylakanoic esters of glycerol for treatment of nitrogen accumulation disorders, portal systemic encephalopathy (also known as hepatic encephalopathy, see EP 1230918 A2, paragraph [0002-0003]), and diseases involving impaired liver function (see: abstract; col. 3, lines 55-60). Glyceryl-tri (4-phenyl butyrate), specifically of claims 7 and 17, is a phenylakanoic esters of glycerol. The reference teaches oral and parenteral dosage forms in amounts from 450 to 600 mg/kg for children and 9.9 to 13 grams/kg for adults (col. 4, lines 53-64), which meets the dosage forms and ranges of instant claims 2, 3, and 11-13.

Regarding the limitation of a method of preventing an initial hepatic encephalopathic episode (of instant claim 1), according to the instant specification (at paragraphs [15-17]) "preventing" can include preventative measures, which is equivalent to a method of treating. In addition, a method of "lessening the severity of" (of claims 21 and 23) or "delaying" (of instant claims 22 and 24) an encephalopathic episode is also a method of treatment. Absent evidence to the contrary, an equivalent outcome is taught by the prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6) Claims 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Majeed KI (*Hyperammonemia*, eMedicine, Internet Access to the Minds of Medicine, December 18, 2001, printed on 5/21/03 from <<http://www.emedicine.com/NEURO/topic162.htm>>, p. 1-22), in view of Harrison's (*Principles of Internal Medicine 10th Edition*, pages 125, 1775, 1781, & 1814-1816).

Majeed teaches that increased entry of ammonia is a primary cause of neurological disorders associated with hyperammonemia, such as congenital deficiencies of urea cycle enzymes, hepatic encephalopathies, Raye Syndrome, several other metabolic disorders, and some toxic encephalopathies. (See: page 2, paragraph 2). The reference teaches sodium benzoate (of instant claims 8, 10, 18 and 20), sodium phenyl acetate (of instant claims 9, 10, 19, and 20), and sodium phenyl butyrate (of instant claims 6 and 16) as urea cycle disorder treatment agents, thus

meeting the limitation of the specific agents. The reference does not teach the limitation that "12 weeks has passed since the person had a prior episode."

Harrison's teaches that "hepatic (portal-systemic) encephalopathy is a complex organic brain syndrome" and "this metabolic disorder of the nervous system may appear in the course of acute or chronic hepatocellular disease or as a complication of portal-systemic venous shunting [and] it may be *acute* and self-limiting or *chronic* and progressive" (p. 1814). The chronic and acute episodic nature of hepatoencephalopathic episodes would include the limitation of 12 weeks passing between episodes (i.e. a patient that has a chronic hepatocellular disease that only occasionally had episodes, for instance once a year, yet is still at risk for episodes due to the chronic nature of their disease). The reference does not teach the agents of the instant invention.

It would have been obvious to one of ordinary skill in the art to have treated a patient at risk for hepatic encephalopathic episodes with the agents of Majeed (i.e. sodium benzoate, sodium phenyl butyrate, etc.) for the treatment of hepatic encephalopathy, having been taught by Harrison's that these episodes can occur as acute or chronic manifestations of hepatocellular disease. In a chronic disease state of the liver, a patient could experience periodic acute episodes of hepatic encephalopathy, therefore the skilled artisan would have been motivated to treat by preventative measures a patient at risk for encephalopathic episodes (i.e. with a chronic liver or metabolic condition as taught by Harrison's), whether the episodes are occurring less than or greater than 12 weeks apart.

Contact Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy A. Lewis whose telephone number is (571) 272-2765. The examiner can normally be reached on Monday-Friday, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Chris Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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